

### REMARKS

Claims 1-24 are pending. Due to a restriction requirement, claims 5-17 have been withdrawn. Claims 1-4 and 18-24 are rejected under 35 U.S.C. § 112, first paragraph. The Office also objects to the Oath and Declaration.

As an initial matter, Applicants respectfully request entry of the amendments and reconsideration of the remarks set forth in Applicants' March 16, 2004 reply (copy enclosed) to the final Office Action mailed on September 16, 2003. Applicants are also adding new claims 25-27 to the application. Thus, for the sake of clarity, the claims shown above under "AMENDMENTS TO THE CLAIMS" again present the amendments made in the March 16<sup>th</sup> reply because, as noted in the Advisory Action mailed on April 14, 2004, these amendments have not yet been entered.

### Claim Amendments

Solely to expedite prosecution, Applicants have canceled non-elected claims 5-17. New claims 25-27 have been added. The new claims find support, for example, in Example 1, beginning at page 9, line 10, of the specification. The remaining claim amendments were presented in Applicants' March 16, 2004 reply and are supported by the specification as noted therein. No new matter has been added by these amendments.

### **Supplemental Oath**

The Office has asserted that the claims “no longer substantially embrace the invention as set forth in the statement of invention and/or the original claims.”

Accordingly, the Office, citing 37 C.F.R. § 1.67(b), states that “applicant is required to file a supplemental oath or declaration.” For the following reasons, Applicants respectively disagree with this requirement as applied to the pending claims. Applicants’ specification clearly describes the claimed invention, and there is no need for the supplemental oath of the inventor because Applicants’ claim amendments do not introduce new matter. *See, e.g., National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230-231, 123 USPQ 279, 283 (6<sup>th</sup> Cir. 1959), *reh’g denied*, 276 F.2d 167 (6<sup>th</sup> Circuit. 1960), *cert. denied*, 362 U.S. 915 (1959) (“Many cases ... have interpreted this Rule [67(b)] to mean that a supplemental oath is not necessary when the amended claims may be fairly derived from the original specifications.”)

### **Rejection under 35 § U.S.C. 112, first paragraph**

#### **Written Description:**

The final rejection of claims 1-4 and 18-24 under 35 § U.S.C. 112, first paragraph, for an asserted lack of written description in the specification was maintained by the Office in the April 14, 2004 Advisory Action for “reasons of record.” In particular, in the final Office Action, the Office asserts that claim 1 encompasses “a virtually limitless

number of fusion proteins” and that the “amino acid composition from one fusion protein to that of another can vary widely.” The Office states (page 4):

The specification has not provided adequate written description of those that fall within the claimed genus such that a skilled artisan would be able to distinguish between those that fall within the claims from those that fall without.

Applicants disagree.

Further to the arguments set forth in Applicants March 16<sup>th</sup> reply to the final Office Action, Applicants point out that claims 4 and 22-24, and new claims 25-27, all of which are directed to particular species of a GCR/ER fusion protein, clearly are described in the specification as filed. In fact, many of these species are not only described in the specification, but have been reduced to practice in the Examples of the instant specification. As claims 4 and 22-27 are not in fact “genus” claims, the written description rejection of these claims is misplaced and should be withdrawn.

Turning to the genus and sub-genus claims, claims 1-3 and 18-21, Applicants submit that they have presented, in their March 16<sup>th</sup> reply, persuasive rebuttal evidence establishing the representative nature of the estrogen receptor to the class of steroid hormone receptors and the G-CSF receptor to the class of cytokine receptors. In terms of supporting the genus (i.e., steroid/cytokine) and sub-genus claims (ER/cytokine or steroid/G-CSF) claims, Applicants note that the standard for adequate written description does not require that the specification describe the exact details for each and every species within the genus described. The standard for adequate written description is whether the

description clearly allows persons of ordinary skill in the art to recognize that one has invented what is claimed (see, e.g., M.P.E.P. § 2163.02 (Eighth Edition, Rev. 2, May 2004)). In applying this standard, the Federal Circuit has held:

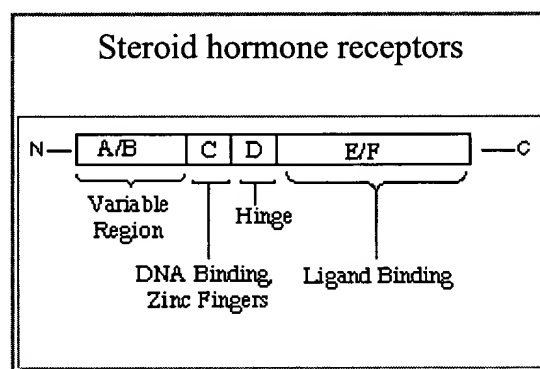
If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 1177, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996).

Applicants further note that, while a variety of species may be needed to demonstrate possession of a substantially variable genus, when the genus is not substantially variable, a limited number of representative species may suffice. What constitutes a representative number is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed (see, e.g., M.P.E.P. § 2163.02(II)(A)(3)(ii) (Eighth Edition, Rev. 2, May 2004)).

In this case, Applicants have demonstrated that the family of steroid hormone receptors is a well-established protein class having known constituents which share commonality of structure and function. In particular, Applicants have provided evidence that steroid hormone receptors evolved from a single ancestral estrogen receptor and, thus, possess both biological similarities and sequence homologies. Accordingly, as the

genus of steroid hormone receptors lacks substantial variation, the disclosed estrogen examples are sufficiently representative to demonstrate possession of the claimed genus.

To further emphasize this point, Applicants note that all steroid hormone receptors are homodimerizing zinc finger transcription factors found exclusively in the cytosol and nucleus. All steroid hormone receptors share regions of close structural and functional homology called domains. From the N-terminal to the C-terminal, these domains correspond to the N-terminal region (A/B domain), DNA binding zinc finger region (C domain), hinge region (D domain), and C-terminal ligand-binding region responsible for binding the particular hormone as well as the second unit of the dimer (E/F domain) (see below). The organization of each domain is conserved in all superfamily members.



See also <http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/S/SteroidREs.html> and <http://www.neurosci.pharm.utoledo.edu/MBC3320/steroids.htm> (Printouts of these websites are provided as Exhibits 1 and 2, respectively.) Thus, contrary to the Office's assertion, given the degree of detail of Applicants' disclosure, particularly the

construction of specific working examples, and the high level of skill and knowledge in the art, a skilled artisan would understand what a ligand-binding domain of a steroid hormone receptor that self-associates upon ligand binding is and could readily distinguish polypeptides that meet this definition from those that do not.

With regard to the second polypeptide, Applicants have affirmatively demonstrated that the cytokine family is a well-established protein class having known constituents that lack substantial variation, particularly with respect to the proliferation-inducing domain. As demonstrated by Applicants, cytokine receptors have significant structural and functional similarities. Not only do cytokine receptors possess a number of conserved sequence motifs and shared structural features, but they also share specific functional similarities, namely the ability to dimerize upon activation. Accordingly, given that the genus of cytokine receptors lacks substantial variation, the G-CSF examples are sufficiently representative to demonstrate possession of the claimed genus.

Finally, even if the Office considers the subject matter of the claims to be broader than that disclosed in the original specification, “the written description requirement may be satisfied if the broader concept ‘would naturally occur to one skilled in the art’ upon reading the earlier specification.” *Levi Strauss & Co. v. Golden Trade, S.R.L.*, 1991 WL 710822 (S.D.N.Y. Dec. 1, 1995).

In sum, given the nature of the invention, the level of skill in the art, the representative nature of the disclosed embodiments, and the degree of guidance set forth

in the specification as to the relevant, identifying characteristics defining members of the claimed genus, the disclosure of the specification would reasonably convey to the artisan that the inventor had possession of the claimed subject matter at the time the application was filed. Thus, Applicants respectfully request reconsideration and withdrawal of the written description rejection.

*Enablement:*

The final rejection of claims 1-4 and 18-24 under 35 U.S.C. § 112, first paragraph, based on the assertion that the specification fails to comply with the enablement requirement was maintained by the Office in the Advisory Action “for reasons of record.” In the final Office Action, the Office states (page 7):

None of the examples teach how the claimed fusion proteins are to be used in a reproducible method.

In response, Applicants again draw the Office’s attention to their March 16<sup>th</sup> reply. Applicants point out, as noted above, that claims 4 and 22-24 (and new claims 25-27) are directed to specific species of GCR/ER fusion proteins, many of which are both explicitly described and reduced to practice in the Examples of the instant specification. Accordingly, because the instant specification describes the construction and application of such fusion proteins in great detail, one skilled in the art would clearly be able to make or use the invention commensurate with claims 4 and 22-27.

Furthermore, as noted in the March 16<sup>th</sup> reply, Applicants remind the Office that a

specification is presumed to be in compliance with the enablement requirement of § 112, first paragraph and, thus, the burden is on the Office to establish a reasonable basis to question enablement. In this case, Applicants submit that the Office has not met this burden. In the final Office Action and the Advisory Action, the Office has failed to support its finding of lack of enablement with scientific reasoning or evidence and, instead, simply makes an unfounded assertion. Furthermore, Applicants rebuttal comments conclusively demonstrate that one reasonably skilled in the art could make and use the claimed a fusion proteins from the disclosures in the patent coupled with information known in the art without undue experimentation. Thus, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.



## CONCLUSION

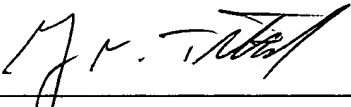
Applicants submit that the application is now in condition for allowance and this action is hereby respectfully requested.

Enclosed with the concurrently filed Request for Continued Examination is a Petition to extend the period for submitting an Appeal Brief pursuant to the Notice of Appeal filed on March 19, 2004, to and including October 19, 2004, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: October 18, 2004

  
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# Steroid Hormone Receptors and their Response Elements

Steroid hormone receptors are proteins that have a binding site for a particular steroid molecule. Their **response elements** are **DNA sequences** that are bound by the complex of the steroid bound to its receptor.

The response element is part of the **promoter** of a gene. Binding by the receptor activates or represses, as the case may be, the gene controlled by that promoter.

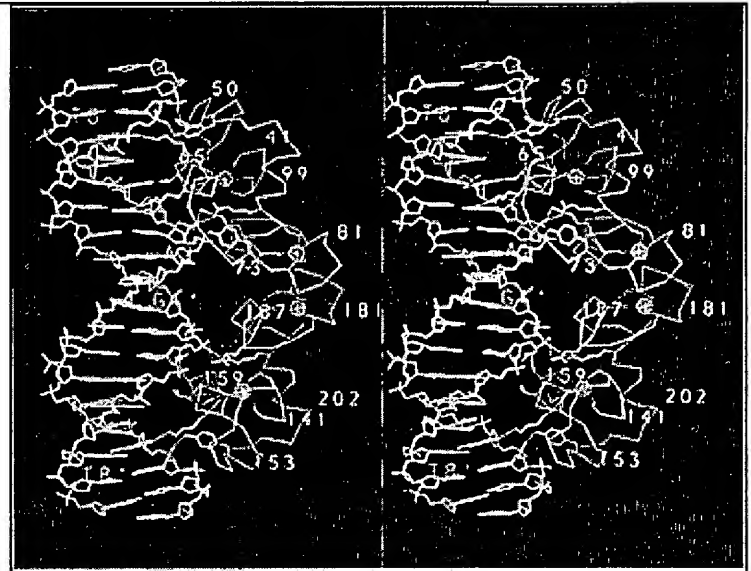
It is through this mechanism that steroid hormones turn genes on (or off).

[Link to general discussion of eukaryotic promoters and the transcription factors that control them.](#)

This image (courtesy of P. B. Sigler) shows a stereoscopic view of the **glucocorticoid response element** (DNA, the double helix shown in yellow at the left of each panel) with the **glucocorticoid receptor** (a protein homodimer, right portion of each panel) bound to it.

The DNA sequence of the glucocorticoid response element is  
**5' AGAACAnnnTGTTCT 3'**  
**3' TCTTGTnnnACAAGA 5'**  
where **n** represents any nucleotide. (Note the inverted repeats.)

The glucocorticoid receptor, like all steroid hormone receptors, is a zinc-finger **transcription factor**; the zinc atoms are the four yellow spheres. Each is attached to four cysteines (shown in dark green).



For a steroid hormone to turn gene transcription on, its receptor must:

- bind to the hormone
- bind to a second copy of itself to form a **homodimer**
- be in the nucleus, moving from the cytosol if necessary
- bind to its response element
- activate other transcription factors to start transcription

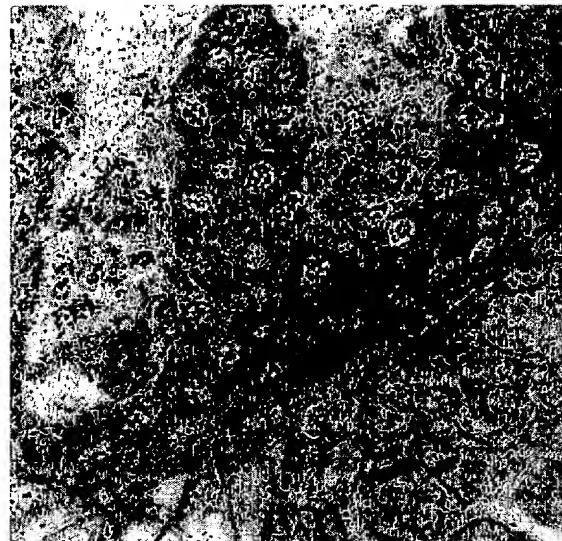
Each of these functions depend upon a particular region of the protein (e.g., the zinc fingers for binding DNA). Mutations in any one region may upset the function of that region without necessarily interfering with other functions of the receptor.

## Visual Evidence of Hormone Binding

This autoradiograph (courtesy of Madhabananda Sar and Walter E. Stumpf) shows the endometrial cells from the uterus of a guinea pig 15 minutes after an injection of radioactive **progesterone**. The radioactivity has concentrated within the nuclei of the endometrial cells as shown by the dark grains superimposed on the images of the nuclei. The same effect is seen when radioactive **estrogens** are administered.

The cells of the endometrium are target cells for both progesterone and estrogens, preparing the uterus for possible pregnancy. [[Link to discussion](#)]

Nontarget cells (e.g. liver cells or lymphocytes) show no accumulation of female sex hormones. Although their DNA contains the response elements, their cells do not have the protein receptors needed.



## The Steroid Hormone Receptor Superfamily

The zinc-finger proteins that serve as receptors for glucocorticoids and progesterone are members of a large family of similar proteins that serve as receptors for

- other steroid hormones like
  - the mineralocoid aldosterone
  - estrogens
- the thyroid hormone, T<sub>3</sub>
- calcitriol, the active form of vitamin D
- relatives of vitamin A

In every case, the receptors consists of at least three functional modules or **domains**. From N-terminal to C-terminal, these are:

- a domain needed for the receptor to activate the promoters of the genes being controlled
- the zinc-finger domain needed for DNA binding (to the response element)
- the domain responsible for binding the particular hormone as well as the second unit of the dimer.

Welcome&Next Search

3 June 2003



## MBC 3320 Steroid hormones and receptors

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### Steroid hormone receptors

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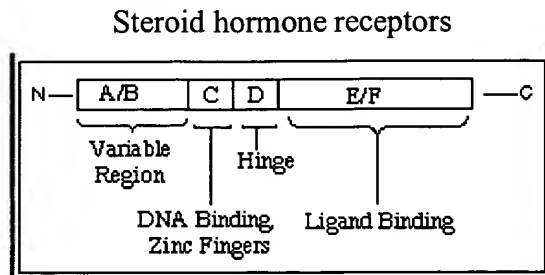
### Steroid hormone receptors

The true nature of the receptors for glucocorticoid and mineralcorticoid hormones, and the differences between hormone receptors, has only recently been elucidated. Much work is in process, and the area is currently one of prime interest to many biotechnology companies. In the next twenty years, some of the most profound advances in drug therapy will come out of the concepts first observed with steroid hormone receptors.

Steroid receptors are proteins found in the cytoplasm or nucleus of eukaryotic cells which bind to and regulate the transcription of DNA under the regulation of steroid hormones. Receptors for the different hormones have strong structural and functional similarities which point to an evolution from a common ancestral gene and therefore are considered a gene superfamily. Representative receptors which belong to this gene superfamily include the DNA binding and regulatory proteins controlled by the steroid hormones estradiol (E2 receptor, ER), cortisol (CORT receptor, GR), androgen (ANDR receptor, AR), progesterone (PROG receptor, PR), and aldosterone (ALDO receptor, MR), the nonsteroid hormones triiodothyronine (T3 receptor, T3R) and dihydroxyvitamin D3 (D3 receptor, VDR), and two classes of retinoid (all-trans retinoic acid and 9-cis retinoic acid) receptors (RARs and RXRs respectively). More than 32 genes encoding at least 75 proteins [receptors can have different isoforms (variations) with different DNA specificity, regulation, or hormone affinity] have been identified as part of this gene superfamily. New members of this superfamily are being reported frequently and include receptors which respond to dioxin. Using new biotechnology, molecular biologists and biochemists have identified protein receptors for which the ligands have not yet been identified, thus giving birth to a class of "orphan receptors".

The hormone gene superfamily can be divided into three functionally distinct subfamilies. These subfamilies are as follows. Type I are classical steroid hormone receptors which include the glucocorticoid receptors (GR, including CORT receptor), androgen receptors (AR), mineralcorticoid receptors (MR, including ALDO receptor), and progesterone receptor. Type II consists of thyroid hormone related receptors including T3R, RAR, RXR, and VDR. Type III is formed by the ER (estrogen receptor) and a few orphan receptors.

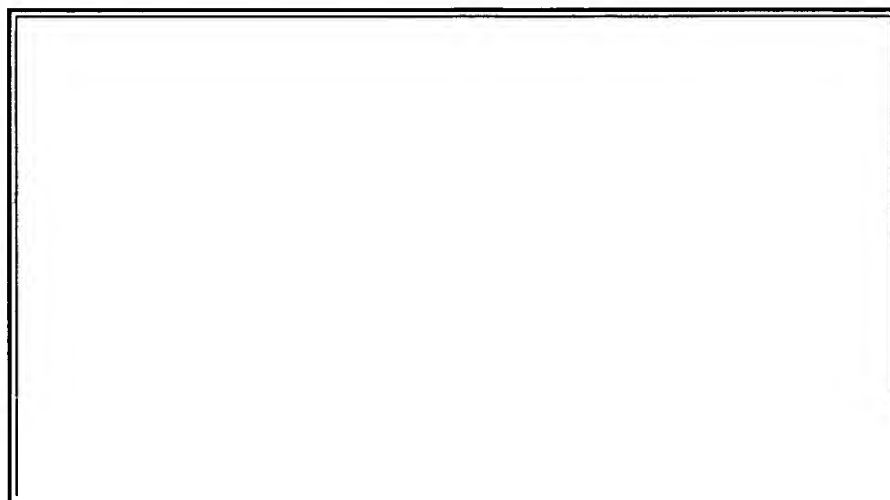
Steroid receptors (proteins) share regions of close structural and/or functional homology which are called domains. For steroid receptors, these domains correspond to the N-terminal region (A/B domain), DNA binding zinc finger region (C domain), hinge region (D domain) and C-terminal ligand-binding region (E/F domain) (see below). The organization of each domain is conserved in all superfamily members.



The DNA which is targeted by the receptors contains specific sequences of DNA which are termed hormone response elements (HREs). These response elements bind two receptors at a time. The receptors bound may be the same protein, in which case the HREs bind homodimers. If the receptor dimers are made up of two different receptors (such as one T3 receptor with one RAR receptor, then the HREs are said to bind heterodimers. Consequently, transcription of DNA which is regulated by a homodimer can be regulated by a single hormone, while DNA binding a heterodimer could be regulated by two separate hormones. Type I (glucocorticoid receptor subfamily) and estrogen (Type III) receptors are associated with heat shock proteins (hsp's) in the absence of hormone and require the hormone (which is termed "ligand") to homodimerize and bind to their DNA response elements. In contrast, Type II receptors (thyroid/retinoic acid receptors) do not associate with heat shock proteins and can bind DNA in the absence of hormone (ligand). Type II may bind as homodimers or heterodimers in what appears to be a response element dependent fashion. The importance of such observations as now conceived is that drugs designed to act as agonists or antagonists of a particular hormone receptor may have differing efficacy or effects on protein transcription depending upon the possibility of a receptor binding to some protein HREs as homodimers and other HREs as heterodimers. The implications are enormous and considerable research must still be done. This line of thinking, possible only since the early 1990's (so don't look for it in the earlier literature) adds another level at which to think about drug regulation of cellular processes. The effect of steroid hormones may not be mediated by just the binding to a single protein receptor, but may be influenced by the binding of that receptor to other receptor proteins and to DNA.

## Type I (or III) Steroid Hormone Receptor

### Type I (steroid) and Type III (estradiol) Receptor Function



Title: FUSION PROTEIN THAT IMPARTS SELECTIVE...

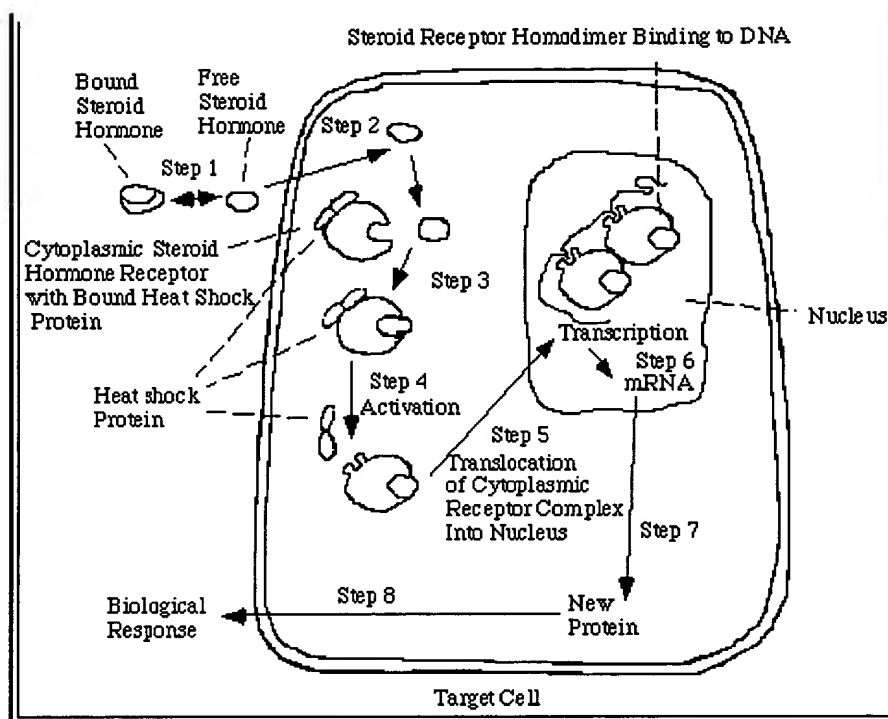
Applicants: Kei-ya Ozawa et al.

Application Serial No. 09/142,305 Filed September 10, 1999

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EXHIBIT 2

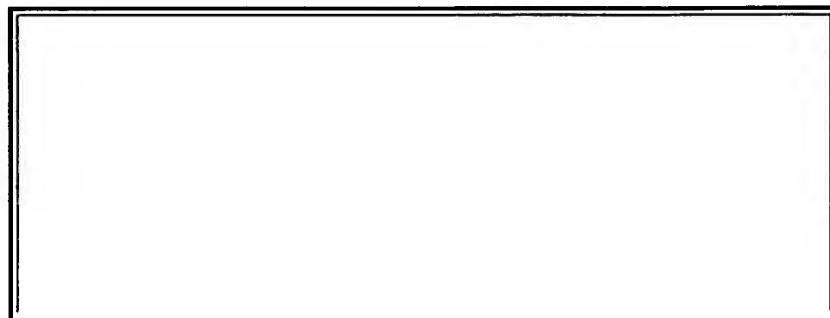
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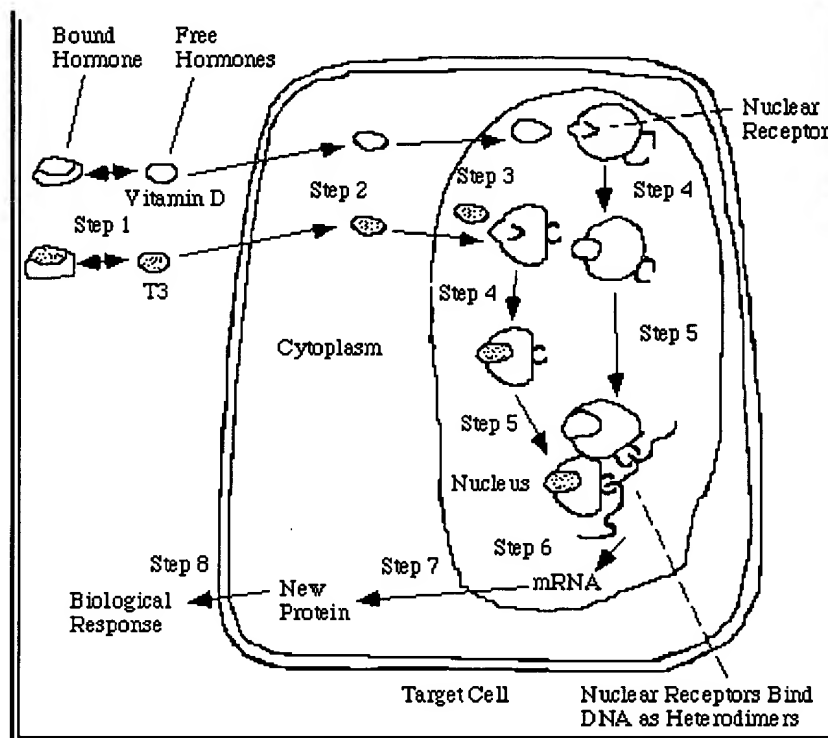


1. Dissociation of Steroid from Binding Protein
2. Transport of Steroid into Cell, Formation of Binding Steroid
3. Binding of Steroid (Testosterone, Progesterone, Estrogen) to Cytoplasmic Receptor with Bound Heat Shock Protein
4. Loss of Heat Shock Protein forms "Activated" Receptor
5. Activated Cytoplasmic Receptor Enters Nucleus, Binds DNA Response Elements as Homodimers.
6. DNA transcribed into messenger RNA
7. mRNA leaves nucleus, translated into protein on cytoplasmic ribosomes
8. Newly made proteins elicit biological response

## Type II Receptors

Type II (Vitamin A and D, Thyroid hormone) Receptor  
Function





1. Dissociation of Hormone from Binding Protein
2. Transport of Hormone into Cell Cytoplasm
3. Transport of Hormone into Nucleus
4. Binding of Hormone to Nuclear Receptor "Activates" Receptor for Binding (note- No heat-shock protein!).
5. Activated Nuclear Receptor Binds DNA Response Elements as Heterodimers.
6. DNA transcribed into messenger RNA
7. mRNA leaves nucleus, translated into protein on cytoplasmic ribosomes
8. Newly made proteins elicit biological response

How do hormones enter a cell, regulate DNA transcription (DNA to messenger RNA), and achieve biological responses? Examine the above cartoons. In the blood, hormones circulate bound to protein. When they contact a cell, the hormones are transferred from the carrier protein, through the plasma membrane (process not well characterized), and into the cell cytoplasm. Type I ligands (cortisol, testosterone, etc.) and estrogen (estradiol) bind to their receptors (which are associated with a heat shock protein) in the cytosol. Once bound to the receptor, the receptor dissociates from its heat shock protein and becomes "activated". The activated receptor moves into the nucleus. Once in the nucleus, the activated receptor either dimerizes then binds or binds sequentially to its corresponding hormone receptor elements (HREs) and can turn on or off transcription of the particular DNA to which it has bound. What effect an activated receptor has on its target DNA appears dependent upon the relationship of its HREs to other DNA elements and transcription factors for that particular DNA. For ligands which bind to Type II receptors, such as vitamin D, thyroid hormones (T3) and retinoids (Vitamin A), the hormones dissociate from blood carrier proteins, move through the plasma membrane, through the cytoplasm, and then into the nucleus without binding any receptors. Once in the nucleus, these hormones then bind to appropriate Type II nuclear receptors to cause receptor activation. Activation for

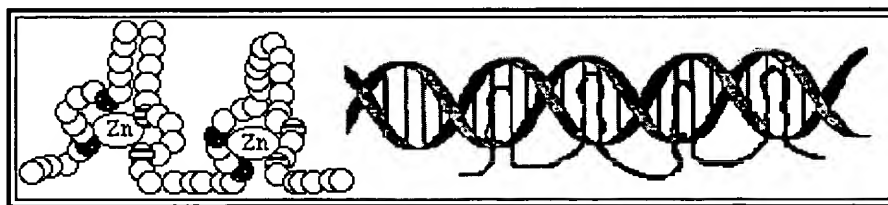
a Type II receptor may lead to homo- or hetero-dimerization and then DNA binding. In one case for the retinoic acid receptor which binds all-trans retenoic acid (an RAR type), the DNA response element binds two receptors of the same type (homodimer) in the presence of all-trans retenoic acid ligand and represses DNA transcription. In the presence of T3 (triiodothyronine), one receptor for T3 exchanges with one receptor of bound RAR to produce an RAR/T3 receptor heterodimer. The heterodimer turns on the DNA transcription. Transcribed messenger RNA in the nucleus moves to the cytosol where it is translated on ribosomes into protein.

Various scenarios for how these hormone receptors interact, and in what order, will prove important in the future to being able to control the synthesis of messenger RNA for one protein in the presence of another even though the transcription of both is regulated by the same ligand. Thus, the synthesis of one protein can be turned on and another turned off in response to the same hormone. One can imagine isoforms of receptors with different ligand affinities which will regulate the synthesis of proteins in a hormone concentration dependent manner. Some proteins may be synthesized at low concentrations as activated by high affinity receptors while others may be turned on or off at higher concentrations when binding to lower ligand affinity receptors takes place.

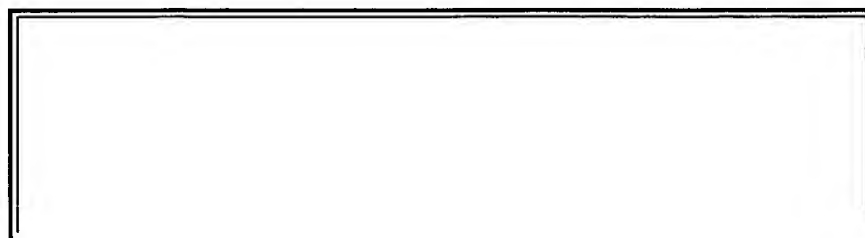
Transcribed messenger RNA in the nucleus moves to the cytosol where it is translated on ribosomes into protein.

With an appreciation of how hormone receptors can control DNA transcription which leads to protein synthesis, let us look at the functions of the domains of the steroid hormone receptor. Refer back to the diagram on page 48 of these notes.

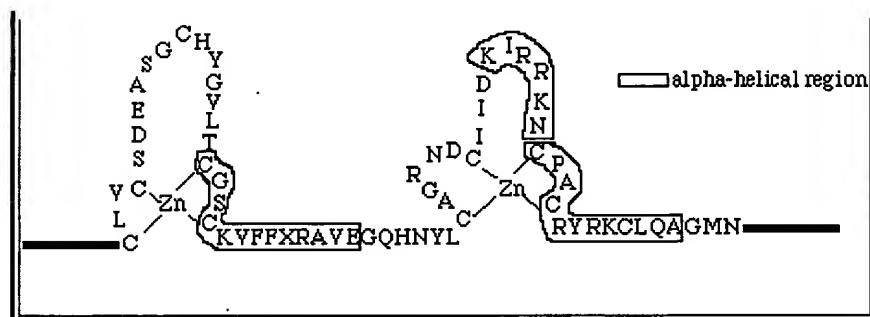
The best characterized domain of the steroid hormones is the C domain. The C domain contains zinc fingers. Zinc fingers are regions of protein which form a three dimensional structure in which two cysteines and either two histidines or cysteines are orientation so as to bind a zinc atom (see "A" and "C" below). The resulting three dimensional protein structure of the zinc finger is shaped so that it can insert between specific base pairs of a DNA helix (see "B" below). The sequence of DNA base pairs into which it can insert is determined by amino acids in and near the zinc bound protein region, and thus such DNA-protein binding is specific (not random).



Left. Zincs Covalently Bound to 2 Cysteines (solid) and 2 Histidines or Cysteines (striped) to form zinc fingers. Right. Protein zinc fingers binding DNA helix.





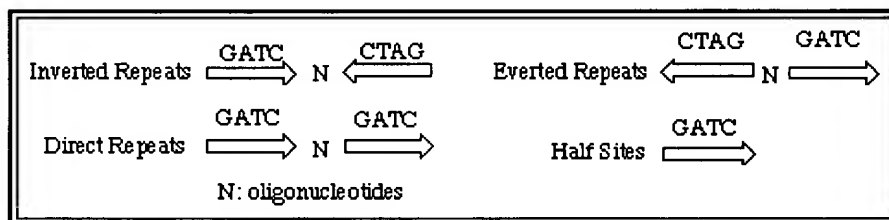


Amino acids responsible for sequence specific recognition in the glucocorticoid receptor.

Another feature of the steroid hormone receptors of Type I and estrogen which has been identified is the nuclear localization sequence. This sequence permits the receptor with bound hormone (ligand) to translocate from the cytosol to the nucleus. These sequences are composed of seven (7) amino acids which overlap the C-terminal end of the DNA binding region (domain C) and the N-terminal hinge region (domain D).

While features of the steroid hormone (ligand) binding region (E/F domains) have been elucidated, as well as contributions of the A/B domain which effect transcriptional activation (also called transactivation), significant work still needs to be done.

X-ray crystal structure data for fully intact steroid hormone receptors is not yet available. X-ray structures of partial zinc finger regions have been obtained. NMR studies of receptors with bound DNA have yielded information useful in deciphering whether receptors are binding as homodimers or heterodimers.



An additional note on the target DNA hormone response element (HRE) sequences in the target DNA. Because each HRE recognizes a protein dimer, each is formed of two DNA binding regions each of which binds to one receptor (each DNA region which binds protein is called a half-site). HREs can differ from each other in three significant ways. First, they can differ in nucleotide sequence, second, in the spacing of each protein binding sequence (half-site), and thirdly, in orientation of one binding site to the other (see figure below which illustrates binding site orientation possibilities). Four paradigms for how hormone response elements can be configured have been determined as shown. For "A. inverted repeats" a palindrome ("ABC N CBA", where N is one or several nucleotides) is often observed. "C. Everted repeats" can be exemplified by an inverted palindrome (CBA N ABC). Nerve Growth Factor I-B is an example of a receptor which binds to a half-site in some cases, and forms heterodimers in others.

The isolation cDNA (cellular DNA) in 1985 encoding for the human glucocorticoid receptor and in 1987 for the human mineralcorticoid receptor revealed oligonucleotide homologies which have permitted the identification and isolation of

cDNA encoding for other receptors through techniques of cDNA library screening.

Classical methods in biochemistry to characterize receptors are still important. As an example of how to isolate receptors from crude cells (when one does not have cDNA information), cell components soluble in detergent prepared from crushed cells can be applied to an affinity column containing aldosterone coupled to beads. The receptors for aldosterone bind to the beads ( $K_D \sim 10^{-8}M$ ) and stick to the column. The purified receptors can be recovered from the column by elution with aldosterone solution. There are typically 1000 - 10,000 steroid receptors per cell.

Steroid receptor conformation as it relates to hormone binding (protein E/F domain). Steroids usually have no net charge or charged functional groups. This means that only weaker Van der Waals and hydrogen bonding forces hold the steroid hormone in its receptor ( $K_D \sim 10^{-8}M$  compared to  $K_D \sim 10^{-11}-10^{-14}M$  if ionic interactions present). The flip side of this is that similarly weak forces hold steroid molecules when held together in crystals. One may expect that the conformation of steroid hormones obtained from X-ray crystal structures should approximate the hormone conformations adopted when binding to its receptor. Such information can be used to facilitate computer modeling and "rational" drug design.

Steroid receptors promote the synthesis of what kinds of proteins? The mRNA transcribed may be for an enzyme which permits the production of another protein or a chemical messenger. This other protein or messenger may control the responses of which the particular cell is capable. Instead of promoting the synthesis of a particular mRNA, the binding of receptor to DNA could result in the inhibition of transcription for a particular mRNA. Thus, the net effect may be a combination of transcriptional upregulation for proteins enhancing a particular cellular response while contradictory or unnecessary protein synthesis would be inhibited. Steroid hormone receptors have been shown to increase the level of activity of tyrosine transaminase, alanine transaminase, and glycogen synthetase in liver cells by as much as 150%. The response takes 24 hours to become effective. In the kidney, aldosterone enhances the synthesis of proteins in the mucosal barrier which regulate permeability to  $Na^+$ . The ovarian cycle is an excellent example where the glucocorticoid receptors for estradiol and progesterone are involved in programmed cell death. One of the actions of estradiol on the corpus luteum of the uterine lining is to upregulate the production of progesterone receptor. The increased number of progesterone receptors increases the control of progesterone over protein synthesis in the corpus luteum. In the absence of fertilization, hormone levels drop. In the absence of hormone, protein synthesis controlled by estradiol and progesterone ceases and the cells die.

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## References

1. Principles of Medicinal Chemistry. by Foye, W.O., T.L. Lemke and D.A. Williams. Williams & Wilkins. Fourth Edition, 1995.
2. Much of the material presented here was developed by Dr. Steve Peseckis, Assistant Professor of Medicinal and Biological Chemistry at The University of Toledo.

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*This page was produced by Dr. William S. Messer, Jr., Professor of Medicinal and Biological Chemistry at The University of Toledo.*

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